Haematuria

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Declaration of Interests

• Jon Rees has received Consultancy and Speaker fees for Ferring and Astellas and is Chair of PCUS
SO, YOU'RE A DOCTOR.

THAT'S RIGHT.

SO, DO YOU SPECIALISE, OR ARE YOU JUST A G.P.?

I SPECIALISE IN AWESOMENESS:

I'M A G.P.
For a Sore Bladder.

Dissolve 1-2 lib. of Sugar Liquorice among Water, about 1 Pint: Drink this in one day, making three divisions or intervals. Probatum Est.

For Pissing Blood.

Take 1-2 Ounce of Nutmeg, 1 Ounce Dandelion Roots, and 1 Ounce Sow Thistle Roots: Make all into one Poudre; then take as much of said Poudre as will ly on a Shilling, each Morning, in a Pint of Cows Milk, that is, a Scots Mutchkin. Do this for 7 days, then by said time, the Poudre will be done, and you will be whole. Otherwise, take the Stones of a Hare boiled or roasted in any meat.

Probatum Est.

For Venemous Bittings.

1-2 Lib. of Garlic bruised and applied, or Olleum Petre, alias Parmala.
Referrals to Haematuria Clinic

– 50:50 between Macro and Microscopic
– Annual cost to NHS £33M
– 1/3 of the £100M cost of treating Bladder Ca
## Presentation of bladder cancer

<table>
<thead>
<tr>
<th>Symptom</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frank Haematuria</td>
<td>162</td>
<td>67</td>
</tr>
<tr>
<td>Pure LUTS</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>Chance</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Symptomatic Microscopic Haematuria</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Symptoms of UTI</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Clear delay in reporting FH</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Gynae bleeding</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Malaise</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Non-specific Sx</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Asymptomatic Microscopic Haematuria</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Incontinence</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Recurrent UTIs</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Anaemia</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>240</td>
<td>100</td>
</tr>
</tbody>
</table>
Terminology

- Macroscopic / Frank / Gross = **VISIBLE** haematuria

- Microscopic / Dipstick = **NON-VISIBLE** haematuria

- **Symptomatic non-visible haematuria** = plus LUTS or upper urinary tract symptoms e.g. loin pain (versus Asymptomatic)
Visible haematuria (VH)

Non-visible haematuria (NVH)

Symptomatic non-visible haematuria (s-NVH)

Asymptomatic non-visible haematuria (a-NVH)

Forget microscopy + cytology

Exclude vigorous exercise, trauma, menstruation, sexual activity, viral illness or UTI.

Also abnormal colouration e.g. beetroot, rifampicin.

Storage symptoms plus ≥ 1+ dipstick on 2 / 3 tests

No symptoms but ≥ 1+ dipstick on 2 / 3 tests
Who to test: Prevalence of NVH

- Approximately 2.5% of general population
- If population screened pick up rate of significant diagnosis only 1.5%
- So ...
Who to test: Indications for a urine dipstick

- LUTS or Upper UT symptoms
- Diagnosis of hypertension
- Diabetes (annual)
- Newly discovered proteinuria
- Newly detected CKD (eGFR<60)
- Multisystem disease with suspected renal involvement
Diagnosis of haematuria

• No evidence for screening

• Exclude transient causes e.g. UTI

• Urine dipstick ‘+’ or more – MSU only to exclude infection

• Symptomatic non-visible haematuria warrants further assessment on single episode

• Asymptomatic non-visible haematuria confirm on 2 out of 3 tests e.g. ‘persistent’
Visible haematuria

- Malignancy relatively common (20 – 25%)

- This study:
  - 72% no disease
  - 16.5% TCC bladder
  - 2% RCC
  - 0.5% UT TCC
  - 9% Stone

Edwards et al, BJU Int 2006
Non-visible haematuria

- Malignancy much less common (3 - 5%)
- This study:
  - 87% no disease
  - 4% TCC bladder
  - 1% RCC
  - 0.1% UT TCC
  - 8% Stone

Edwards et al, BJU Int 2006
Risk of malignancy in non-visible haematuria

- In men under 50 years old: 0.44%
- In women under 60 years old: 0.75%
Risk of malignancy in non-visible haematuria

Prevalence (%) Malignancy in Non-visible haematuria

Edwards et al, BJU Int 2006, based on 4020 patients at haematuria clinic
Causes of NVH

Urological causes

• Common:
  – BPH
  – Cancer (bladder, renal, prostate, ureter)
  – Calculus disease
  – Cystitis / pyelonephritis
  – Schistosomiasis

• Less Common:
  – Radiation cystitis
  – Urethral strictures
  – TB
  – Medullary sponge kidney
  – Polycystic kidney disease
  – Loin pain haematuria syndrome

Nephrological causes

• Common:
  – Thin basement membrane disease
  – IgA Nephropathy

• Less common:
  – Lupus nephritis
  – Vasculitis
  – HSP
  – Goodpastures syndrome
  – Haemolytic uraemic syndrome
  – Alport’s syndrome
  – Nail patella syndrome
  – Chronic primary glomerulonephritis
The Podocyte
Thin basement membrane syndrome

BM usually ~450μm.

In TBMS it is reduced to ~150μm.
Thin Basement Membrane disease

• AKA ‘Benign familial haematuria

• Presents with non-visible haematuria

• Renal function, blood pressure, protein excretion all normal

• No risk to long term renal function so diagnosis not usually confirmed by biopsy
IgA Nephropathy (Berger’s)

- Immunoglobulin deposited in kidneys
- Usually follows simple viral URTI
- Often presents initially with VH, then persistent NVH
- Progresses to chronic renal failure in 25% over 20 years
Decision algorithm for the investigation of non-visible haematuria and the referral criteria adopted by the British Association of Urological Surgeons and the Renal Association

Visible haematuria
- Plasma creatinine estimated GFR
- Exclude transient causes including urinary tract infection

Non-visible haematuria
- Exclude transient causes including urinary tract infection

Symptomatic non-visible haematuria
- Blood pressure
  - Plasma creatinine estimated GFR
  - Send urine for ACR or PCR

<40 years
- Normal
  - All of:
    - Estimated GFR ≥60 ml/min AND
    - ACR <30 or PCR <50 AND
    - Blood pressure <140/90 mm Hg
- Urology assessment
  - Imaging and cystoscopy
  - Cause established

<40 years
- Abnormal
  - Any one of:
    - Estimated GFR <60 ml/min
    - ACR ≥30 or PCR ≥50
    - Blood pressure ≥140/90 mm Hg
- Nephrology assessment
  - Cause established
  - No cause established

Primary care monitoring
- Annual assessment (while haematuria persists) of blood pressure, estimated GFR, and ACR/PCR
- Referral or re-referral to urology if:
  - Development of visible haematuria or symptomatic non-visible haematuria
- Referral to nephrology if:
  - Significant or increasing proteinuria (ACR ≥30 or PCR ≥50)
  - Estimated GFR <30 ml/min*
  - Deteriorating estimated GFR* (by >5 ml/min fall within 1 year, or >10 ml/min fall within 5 years)

*Confirmed on at least 2 readings and without an identifiable reversible cause
Note: Direct referrals between urology and nephrology will depend on local commissioning guides

Investigation: VH

Visible Haematuria VH

BP, eGFR, Urinalysis

Urology (Imaging & cystoscopy)

Very occasionally divert to nephrology

Cause established

No cause established*
Investigation: s-NVH

Visible Haematuria (VH)

Non-Visible Haematuria (NVH)

Symptomatic non-visible Haematuria (s-NVH)

Asymptomatic non-visible Haematuria (a-NVH)

BP, eGFR, Urinalysis

Urology (Imaging & cystoscopy)

Cause established

No cause established*

Very occasionally divert to nephrology
Risk of urological malignancy

- Variable risk but increased in:
  - Smokers
  - Age > 50 male; > 60 female
  - Male > Female
  - History of urological disorder or disease
  - History of storage symptoms / UTI
  - Exposure to benzene / aromatic amines
    - Rubber, textiles, cable, printing
  - Pelvic irradiation
Investigation: a-NVH

Asymptomatic non-visible haematuria a-NVH

Age >40 (?50)
- BP, eGFR, Urinalysis
  - Urology (Imaging & cystoscopy)
    - Cause established

Age <40 (?50)
- Normal
  - BP <140/90
  - eGFR >60
  - ACR <30
    - Urology (Imaging & cystoscopy)
    - Cause established

- Abnormal
  - BP >140/90
  - eGFR <60
  - ACR >30
    - Nephrology
    - Cause established

*No cause established
Monitoring of Haematuria

No cause established

Primary Care Monitoring

Annual assessment while haematuria persists of BP, eGFR & ACR

Refer or re-refer to urology if:
- Development of VH or s-NVH

Refer to nephrology if:
- Significant or increasing proteinuria (ACR > 30)
- eGFR <30 on 2 readings without an identifiable reversible cause
- Deteriorating eGFR (1 year fall >5ml/min, or >10ml/min in 5 years)
2015

National Collaborating Centre for Cancer

Suspected cancer:
recognition and management of suspected cancer in children, young people and adults

Clinical Guideline
Full guideline
November 2014
Bladder cancer

- 10,000 new cases p.a. in UK
- Full time GP diagnoses new case every 3-5 years
- 75% of new cases are male
- 5 yr survival = 55%

Renal cancer

- Over 10,000 new cases p.a. in UK
- Full time GP diagnoses 1 new case every 3-5 years
- 60% of new diagnoses in males
- 5 year survival >55%
NICE 2005 Suspected Cancer CG27

- Patients with painless macroscopic haematuria should be referred urgently at any age
- Patients with symptoms suggestive of UTI with macroscopic haematuria should be referred urgently if infection not confirmed
- Patients 50 years or over with unexplained microscopic haematuria should be referred urgently
- Patients under 50 with normal creatinine and no proteinuria should be referred routinely to a urologist
NICE recommendations 2015

Visible & Unexplained, without UTI or that persists or recurs after successful Rx of UTI, 45 & over
  – 2ww ref - ?Bladder / Renal

Non-visible & Unexplained, with dysuria or raised WCC, 60 & over
  – 2ww - ?Bladder

Visible with low Hb or thrombocytosis or high blood glucose or unexplained vaginal discharge, women 55 & over
  – Direct access pelvic USS - ?Endometrial

Visible, in men
  – Consider PSA & DRE - ?Prostate
Urological

Prostate cancer

**Urgent referral:**
Urgently refer men (appointment within two weeks) if either:
- Their prostate feels malignant on digital rectal examination (DRE)

**OR**
- Their prostate specific antigen (PSA) levels are above the age-specific reference range.

**Non-urgent investigation:**
Consider a PSA test **AND** DRE in men with any of the following:
- Any lower urinary tract symptoms, such as nocturia, urinary frequency, hesitancy, urgency or retention
- Erectile dysfunction
- Visible haematuria.

**Accompanying notes:**
Prostate-specific antigen ranges:
- 40–49 years 0–2.5ng/L
- 50–59 years 0–3.5ng/L
- 60–69 years 0–4.5ng/L
- 70–79 years 0–6.5ng/L

Consider alternative contributing factors that may influence an individual's PSA ranges.

Bladder cancer

**Urgent referral:**
Urgently refer patients (appointment within two weeks) if they are:
- Aged 45 and over with either:
  - Unexplained visible haematuria without urinary tract infection

**OR**
- Visible haematuria that persists or recurs after successful treatment of urinary tract infection.
- Aged 60 and over with unexplained non-visible haematuria and either:
  - Dysuria

**OR**
- A raised white cell count on a blood test.

**Non-urgent referral:**
Consider referral in patients aged 60 and over with recurrent or persistent urinary tract infection that is unexplained.

Renal cancer

**Urgent referral:**
Urgently refer patients (appointment within two weeks) if they are:
- Aged 45 years and over with either:
  - Unexplained visible haematuria without urinary tract infection
  - Visible haematuria that persists or recurs after successful treatment of urinary tract infection.

Testicular cancer

**Urgent referral:**
Consider urgent referral (appointment within two weeks) in men with any of the following changes in the testis:
- Non-painful enlargement
- Change in shape
- Change in texture.

**Direct access ultrasound:**
Consider a direct access ultrasound scan in men with unexplained or persistent testicular symptoms.

Penile cancer

**Urgent referral:**
Consider urgent referral (appointment within two weeks) in men with any of the following, after exclusion of sexually transmitted infection as a cause or after treatment for a sexually transmitted infection has been completed:
- A penile mass
- An ulcerated lesion
- Unexplained **OR** persistent symptoms affecting the foreskin or glans.
Scenario 1

Paul, a 39 year old, is a type 2 diabetic, and found to have non-visible haematuria by your practice nurse. He has had the dipstick repeated 2 weeks after it was initially found and he again had a positive dip result. His last diabetic review was a month ago – his HbA1c is well controlled at 52. He has an eGFR of 50mls/min, an ACR of 45mg/mmol, and a blood pressure of 138/78. His eGFR has deteriorated slightly since the previous result, 12months ago, of 62mls/min.

What would be your next step?
Scenario 2

Markus, who is 25 years old, has come to see you as part of the morning surgery. He explains that the nurse in the occupational health department at work told him to see his GP as he was found to have non-visible haematuria during a routine medical at work. He has no symptoms, is usually fit and well, and is training for a marathon at present. Markus has not been taking any new medication. His father was diagnosed with ischaemic heart disease aged 52.

What would you do next?
Scenario 3

Amrita, a 54 year old teacher has been to see the practice nurse for a new-patient appointment and was found to have 3+ blood on a urine dipstick. The nurse comes to discuss her case with you. Amrita has no known medical conditions and is asymptomatic.
What are your next steps?
Scenario 4

Ben, a 64 year old with well-controlled hypertension comes to see you with LUTS of dysuria and increased daytime frequency. He is an ex-smoker with no relevant family history. You perform a urine dip test which shows Hb2+, leuc 1+.

What will you do now?
Scenario 5

• Jackie, a 65 year old retail assistant, was seen last week in the haematuria clinic of your local urology department. She had a flexible cystoscopy and renal ultrasound to investigate newly discovered non-visible haematuria. Both investigations were completely normal. She was not told whether she requires any further monitoring and has come to see you to seek advice on this.

• What would you advise?